a'2 contd

alkoxy, allyloxy, and aryloxy, and[may include] having from one to twenty carbon atoms.

REMARKS

Claims 1-15 are pending in the captioned application. Applicants have amended Claims 6 and 8 in response to the Examiner's rejections. Applicants respectfully assert that the claims, as amended, are fairly based on the specification and respectfully request their entry.

The Examiner has rejected Claim 6 under 35 U.S.C. 112, second paragraph, as Being indefinite for failing to particularly point out and distinctly claim the subject which Applicant provides us the invention". Specifically, the Applicant notes in the last line of the claim "The term phospate is technically incorrect. Did Applicant intend to end the claim with the term group or the term moiety?" In response, Applicants have amended Claim 6 to recite group at the end. Applicants respectfully submit that this overcomes the Examiner's rejection and that it should not be withdrawn.

The Examiner has also rejected Claim 8 under 35 U.S.C. 112, second paragraph, for the recitation of the term "may include from one to twenty carbon atoms", which the Examiner states "is open ended language which fails to properly define the metes and bounds of the instant claim".

In response, Applicants have amended the claim to more unambiguously state that the hydrocarbon groups may contain from 1-20 carbons. Applicants respectfully submit that this rejection overcomes the Examiner's rejection, which should be withdrawn.

The Examiner has rejected Claims 1-14 under 35 U.S.C. 102 (b), as being anticipated by Hsiung et al. (US Patent No. 4,426,517). Specifically, the Examiner states "The process of oglionucleotide and polynucleotide de-cyanoethylation disclosed by

Hsiung et al. relies on diethylamine to remove both cyanoethyl substituents and to scavenge the resultant acrylonitrile because the reagent is capable of acting, and is assumed to have acted, both as a basic reagent and a biproduct scavenger. In addition, the failure of the Applicant to clearly define cleaving reagent and its site of action (no product structure has been clearly defined), the instant claims are deemed to include the possibility of no process step requiring a 'cleaving reagent', a possibility required by Claim 35 wherein the oligomer must be in solution so no cleavage from a solid support is either possible or necessary".

In response, Applicants respectfully submit that the Examiner has misunderstood that disclosure of the Hsiung et al. reference. The Applicants concede that the Hsiung et al. reference does disclose the use of organic amines to remove cyanoethyl moieties from triesters, which are intermediates in oglionucleotide synthesis. However, Applicants respectfully submit that the patent discloses that this is done in solution, and no reference is made as to whether this process should be run, or even if it would occur, when the oglionucleotide is attached to a substrate. Further, Applicants respectfully submit that Hsiung provides no discussion relating to modification of bases by released acrylonitrile. Selective removal of cyanoethyl blocking group by treatment of the polynucleotide with diethylamine does not automatically guarantee the prevention of such base modification unless the time of contact between the amine solution and the nucleotide is taken into consideration and kept at a minimum. Such is not addressed by the reference.

Because of this, Applicants respectfully assert that the Hsiung et al. patent neither discloses, nor even suggests the instant invention wherein oglionucleotide is attached to a substrate and the phosphate protecting groups are removed without detaching the

oglionucleotide from the substrate. In the absence of such disclosure, Applicants respectfully assert that the Examiner's rejection under 35 U.S.C. 102 (b) cannot be sustained and should be withdrawn.

The Examiner has rejected Claims 1-15 under 35 U.S.C. 103 (a) as being unpatentable over Hsiung et al. in view of Pfleiderer et al. (US Patent No. 5,936,077). Specifically, the Examiner states "The instant claims are related directed to a method of deprotecting the O-protected phosphotriesters of oglionucleotides by contacting the same with an organic amine, particularly diethylamine". The Examiner continues "Hsiung et al. discloses the use of organic amines diethylamines, and particular to remove the cyanoethyl moiety from phosphate triesters which were intermediates in oglionucleotide synthesis". The Examiner concedes "Hsiung et al. does not specifically detail the application of this process to support and bound oglionucleotides or include a second process of detachment from the solid support", but states "Pfleiderer et al. discloses that the paragraph describing Example 9 the contacting of a support bound oglionucleotide with a mixture of amines including piperidine to effect deprotection of the support bound oglionucleotide which is subsequently detached from the solid support by contacting the same with ammonia. Pfleiderer et al. does not disclose the selective de-cyanoethylation of solid-support bound oglionucleotides".

The Examiner concludes "It would have been obvious to a person having ordinary skill in the art at the time the invention was made to apply the methodology of Hsiung et al. to the deprotection support bound oglionucleotides like those found in Pfleiderer et al. because the disclosure of the selective deprotection by Hsiung et al. very closely analogous to the deprotection scheme of Pfleiderer et al.". The Examiner continues "One

having ordinary skill in the art would have been motivated to combine these references because Pfleiderer etal. Also uses amines to deprotect both phosphate and amino groups. Therefore, the instant claimed porotecc [sic.] of selective phosphate deprotection would have been obvious to one of ordinary skill in the art having the above cited references before him at the time the invention was made".

In response, Applicants reiterate the points made in the arguments distinguishing Hsiung et al. reference above, and respectfully submit that the addition of the Pfleiderer et al. reference does nothing to remedy these deficiencies. Specifically, the Pfleiderer et al. reference recommends the use of special protecting groups like cyclic diacyl (phthaloyl) on exocyclic amino groups on nucleo-bases to enable the process to work. No specific guidance is given to determine if the same scheme would work on standard nucleo-base protecting groups like benzoyl, acetyl, phenoxyactyl, etc. or not.

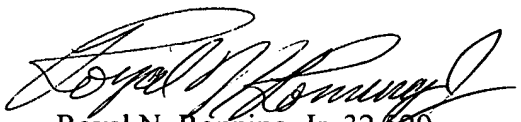
Further, the reference discloses the use of diazabicyclo (5.4.0.)undec-7-ene (DBU) as the base of choice for selectively removing the protecting group, and presumably cyanoethyl phosphate protecting groups as well. Pfleiderer et al. also recommend that non-nucleophilic bases such as lutidine will also remove such protecting groups, something Applicants respectfully assert is the case. Included, such is contrary to the experimental observations common to any petitioner in the art since in the capping step employed during solid phase a construction of oglionucleotides, lutidine is one of the bases of choice used in the process to acylate to free hydroxyl groups. Since all of the exocyclic amino protecting groups and cyanoethyl phosphate protecting groups remain intact during this exposure by the capping reagents containing lutidine, it would be understood by one skilled in the art that lutidine could not be used in this context.

Because of this, Applicants respectfully submit that the reference merely discloses the use of DBU is under special circumstances where the nucleobases are protected by cyclic diacyl protecting groups. Applicants respectfully assert that, based on Pfleiderer's teachings, it is not obvious that diethylamine would selectively decyanoethylate phosphate protecting groups or whether group tethering the oglionucleotide to the substrate would be stable to such treatment, since diethylamine is more nucleophilic than DBU and could potentially hydrolize succinate linkages used generally to tether the oglionucleotides.

In view of the foregoing, Applicants respectfully assert that the Examiner's rejection cannot be sustained and should be withdrawn.

In view of the foregoing, Applicants respectfully assert that the Examiner's rejection cannot be sustained, and should be withdrawn. Applicants believe that the claims, as amended, are an allowable form and earnestly solicit the allowance of Claims 1-15.

Respectfully submitted,



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Amended Claims (marked up copy showing amendment(s))

6. (once amended) The method of Claim 5, wherein the phosphate protecting group is a 2-cyanoethyl phosphate group.

8. (once amended) The method of Claim 1, wherein the reagent used to selectively remove phosphate protecting groups is an amine with a formula R-N-R_1R_2 wherein R, R_1 and R_2 are independently hydrogen, hydroxy, or a hydrocarbon selected from the group consisting of alkyl, allyl, aryl, cycloalkyl, alkenyl, alkoxy, allyloxy, and aryloxy, and[may include] having from one to twenty carbon atoms.